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PATENT COOPERATION TREATY

REC'D 21 SEP 2000

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 018413-191	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/US99/09488	International filing date (day/month/year) 28 APRIL 1999	Priority date (day/month/year) 28 APRIL 1998
International Patent Classification (IPC) or national classification and IPC IPC(7): A61M 25/00 and US Cl.: 604/525, 526		
Applicant MICRO THERAPEUTICS, INC.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 3 sheets.
- ☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority. (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).
- These annexes consist of a total of 0 sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☐ Non-establishment of report with regard to novelty, inventive step or industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand 03 NOVEMBER 1999	Date of completion of this report 31 MAY 2000
Name and mailing address of the IPEA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	Authorized officer SHARON KENNEDY Telephone No. (703) 305-0154
Facsimile No. (703) 305-3230	Sharon Kennedy Primary Examiner

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/US99/09488

I. Basis of the report1. With regard to the **elements** of the international application:*☒ the international application as originally filed☒ the description:

pages 1-16 , as originally filed
pages NONE , filed with the demand
pages NONE , filed with the letter of _____

☒ the claims:

pages 17-19 , as originally filed
pages NONE , as amended (together with any statement) under Article 19
pages NONE , filed with the demand
pages NONE , filed with the letter of _____

☒ the drawings:

pages 1 , as originally filed
pages NONE , filed with the demand
pages NONE , filed with the letter of _____

☒ the sequence listing part of the description:

pages NONE , as originally filed
pages NONE , filed with the demand
pages NONE , filed with the letter of _____

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is:☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).☐ the language of publication of the international application (under Rule 48.3(b)).☐ the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:☐ contained in the international application in printed form.☐ filed together with the international application in computer readable form.☐ furnished subsequently to this Authority in written form.☐ furnished subsequently to this Authority in computer readable form.☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.4. ☒ The amendments have resulted in the cancellation of:☒ the description, pages NONE☒ the claims, Nos. NONE☒ the drawings, sheets/fig NONE5. ☐ This report has been drawn as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

* Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).

**Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/US99/09488

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**1. statement**

Novelty (N)

Claims 6, 7, 9, 14 YESClaims 1-5, 8, 10-13, 15-19 NO

Inventive Step (IS)

Claims 6, 9, 14 YESClaims 1-5, 7, 8, 10-13, 15-19 NO

Industrial Applicability (IA)

Claims 1-19 YESClaims NONE NO**2. citations and explanations (Rule 70.7)**

Claims 1-5, 8, 10-13 and 15-19 lack novelty under PCT Article 33(2) as being anticipated by Mortier et al. 5,730,733.

Claim 7 lacks an inventive step under PCT Article 33(3) as being obvious over Mortier et al. 5,730,733. The use of chlorinated poly-olefin to manufacture catheters is obvious.

Claims 6, 9 and 14 meet the criteria set out in PCT Article 33(2)-(4), because the prior art does not teach or fairly suggest the tapering strands of claims 6 and 9, nor the hydrophilic coating in combination with the second end of the distal segment being uncoated to improve flexibility as recited in claim 14.

----- NEW CITATIONS -----
NONE

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PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 65798	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. PCT/US 99/ 09151	International filing date (day/month/year) 27/04/1999	(Earliest) Priority Date (day/month/year) 30/04/1998
Applicant ..CENTERS FOR DISEASE CONTROL AND PREVENTION,et.al		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 4 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

- a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

- b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing:

☒ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☒ furnished subsequently to this Authority in computer readable form.

☒ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☒ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. ☒ **Certain claims were found unsearchable** (See Box I).

3. ☐ **Unity of invention is lacking** (see Box II).

4. With regard to the **title**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. _____

☐ as suggested by the applicant.

☐ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention.

☐ None of the figures.

2/11/10

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 99/09151

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 34-38
are directed to a method of treatment of the human/animal
body, the search has been carried out and based on the alleged
effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such
an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all
searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment
of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report
covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is
restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 99/09151

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C12N15/31 C07K14/37 A61K39/00 C07K16/14

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07K C12N A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Abstracts of the 97th General Meeting of the American Society for Microbiology, vol. 97, 1997 XP002121615 Isolation and Characterisation of the M antigen of H. capsulatum. R. M. Zancope-Oliveira et al. page 266 ---	1-40
X,P	R. M. ZANCOPE-OLIVEIRA AT AL.: "Molecular cloning, characterisation and expression of the M antigen of Histoplasma capsulatum" INFECT. IMMUN., vol. 67, no. 4, 1999, pages 1947-1953, XP002119766 the whole document --- -/-	1-40

☒ Further documents are listed in the continuation of box C.☐ Patent family members are listed in annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

4 November 1999

Date of mailing of the international search report

16/11/1999

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Skelly, J

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 99/09151

C:(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	R. M. ZANCOPE-OLIVEIRA ET AL.: "Effect of Histoplasmin M antigen chemical and enzymatic deglycosylation on cross reactivity in the Enzyme-linked immunoelectrotransfer blot method" CLIN. DIAGNOS. LAB. IMMUNOL., vol. 1, no. 4, 1994, pages 390-393, XP002119767 the whole document ---	10-15, 21-26, 39,40
X	EMBL Database, Heidelberg, FRG Accession Number AF026268, 14/11/1997 Zancope-Oliveira: "Molecular cloning, characterization, and expression of the M antigen of histoplasma capsulatum" XP002119768 the whole document -----	1-40

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PATENT COOPERATION TREATY

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25 SEP 2000

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 65798	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/US99/09151	International filing date (day/month/year) 27/04/1999	Priority date (day/month/year) 30/04/1998
International Patent Classification (IPC) or national classification and IPC C12N15/31		
Applicant ..CENTERS FOR DISEASE CONTROL AND PREVENTION,et.al		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.



2. This REPORT consists of a total of 7 sheets, including this cover sheet.

- ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☒ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☒ Certain observations on the international application

Date of submission of the demand 14/10/1999	Date of completion of this report 20.09.2000
Name and mailing address of the international preliminary examining authority:  European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Authorized officer Skelly, J Telephone No. +31 70 340 3413 

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US99/09151

I. Basis of the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

1-56 as originally filed

Claims, No.:

1-40 as originally filed

Drawings, sheets:

1/6-6/6 as originally filed

2. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US99/09151

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	16-20, 28 partially, 31-38
	No:	Claims	1-15, 21-27, 28 partially, 29, 30, 39, 40
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-40
Industrial applicability (IA)	Yes:	Claims	1-33, 39, 40, (34-38 see remark)
	No:	Claims	

2. Citations and explanations

see separate sheet

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

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**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/US99/09151

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

The following documents are considered to be relevant. The numbering will be adhered to for the rest of the procedure:

D1:EMBL Database, Heidelberg, FRG Accession Number AF026268, 14/11/1997
Zancope-Oliveira: 'Molecular cloning, characterization, and expression of the M antigen of *Histoplasma capsulatum*' XP002119768

D2:R. M. ZANCOPE-OLIVEIRA ET AL.: 'Effect of Histoplasmin M antigen chemical and enzymatic deglycosylation on cross reactivity in the Enzyme-linked immunoelectrotransfer blot method' CLIN. DIAGNOS. LAB. IMMUNOL., vol. 1, no. 4, 1994, pages 390-393, XP002119767

D3: US 5352579 (Milliman)

Novelty (Art. 33(2) PCT)

The complete sequences of the *H. capsulatum* M protein and of the DNA encoding it were published in the EMBL database in November 1997 (D1). This disclosure is therefore novelty-destroying for the subject-matter of claims 1-15.

D2 describes the purification of M antigen and its use for detection of antibodies in clinical samples (see especially page 393 last paragraph). Also described are monoclonal antibodies against the M antigen (page 391, col. 1, 4th paragraph). The subject-matter of claims 10-15, 21-28 (partially), 29, 30, 39 and 40 is therefore anticipated by this disclosure.

The subject-matter of the remaining claims 16-20, 28 (partially), and 31-38 is considered to be novel.

Inventive Step (Art. 33(3) PCT)

Inventive step will only be considered for novel subject-matter.

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**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/US99/09151

Claims 16-20 and 31-33 are directed, respectively, to a vector comprising the nucleic acid encoding the M antigen, and to a host containing such a vector, presumably for the purpose of expressing the protein. The incorporation of a known nucleic acid encoding a protein in a vector in order to express in a host it is an obvious, routine alternative to purifying the protein from its natural source and no inventive step can be recognised for this subject-matter.

The subject-matter of claim 28, insofar as it concerns a kit containing a nucleic acid for detection of *H. capsulatum*, also lacks an inventive step. Oligonucleotide sequences from DNA encoding M antigen have been used previously for this purpose (D3). The solution to the problem of providing further sequences for the same purpose is provided by the disclosure of the complete DNA sequence (D1).

The subject matter of claims 34-38, a vaccine comprising the known M protein, and its use in a method of diagnosis, is also not inventive. Such uses are suggested to the skilled man by the fact that M protein is known to be the immunodominant antigen of *H. capsulatum* (see D 2, p. 390, paragraph bridging cols. 1 and 2).

Industrial Applicability (Art. 33(4) PCT)

For the assessment of claims 34-38 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in diagnosis carried out on the human or animal body, but may allow, however, claims to a known compound for first use in diagnosis and the use of such a compound for the manufacture of a diagnostic reagent for a new diagnostic method.

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**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/US99/09151

Re Item VI

Certain documents cited

Non-written disclosures (Rule 70.9)

Kind of non-written disclosure	Date of non-written disclosure (day/month/year)	Date of written disclosure referring to non-written disclosure (day/month/year)
Oral Disclosure	4-8.5.1997	1997

Abstracts of the 97th General Meeting of the American Society for Microbiology, vol. 97, 1997 XP002121615

Re Item VIII

Certain observations on the international application

The following observations are made on the clarity of the claims (Art. 6 PCT).

The expression in claim 1 "An isolated nucleic acid comprising:" means that the nucleic acid *contains* any one of the listed sequences. This means that the parts of the claim directed to "a fragment" also encompass the whole sequence. Moreover, expressions like "a fragment of a nucleic acid having a nucleotide sequence as set forth in the Sequence listing as SEQ. ID. No. 1" can be read as meaning the whole sequence, rather than a fragment thereof.

The expression "substantially the same" is vague and unclear and gives no indication of the degree of similarity that falls within the scope of the claim. Likewise the expression "*essentially* of between 10 and 100 nucleotides" introduces vagueness about the exact length of the nucleic acid concerned.

The conditions specified for hybridisation: "able to form a hybrid at 60°C" are not sufficiently precise.

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**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/US99/09151

The same objections as to lack of clarity apply *mutatis mutandis* to all other claims in which the above-mentioned expressions appear.

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PATENT COOPERATION TREATY

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NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Assistant Commissioner for Patents
United States Patent and Trademark
Office
Box PCT
Washington, D.C.20231
ÉTATS-UNIS D'AMÉRIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 08 November 1999 (08.11.99)	
International application No. PCT/US99/09151	Applicant's or agent's file reference 65798
International filing date (day/month/year) 27 April 1999 (27.04.99)	Priority date (day/month/year) 30 April 1998 (30.04.98)
Applicant ZANCOPE-OLIVEIRA, Rosely, M. et al	

1. The designated Office is hereby notified of its election made:

☒ in the demand filed with the International Preliminary Examining Authority on:

14 October 1999 (14.10.99)

☐ in a notice effecting later election filed with the International Bureau on:

2. The election ☒ was
☐ was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

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The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Lazar Joseph Panakal
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

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